

## REMARKS

### Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The 5 attached page is captioned "Version with markings to show changes made."

### Oath/Declaration

The Examiner stated that the oath or declaration is 10 defective because each copy of the oath fails to list all of the inventors. Applicants respectfully disagree.

The name of co-inventor Curiel was listed in co-inventor Tillman's declaration that was filed together with the specification, and the name of co-inventor Tillman was listed in co-inventor 15 Curiel's declaration that was filed together with the specification. Applicants hereby submit copies of the filed declarations and respectfully submit that the declarations filed together with the specification were in compliance with 37 CFR 1.63.

The 35 U.S.C. §112 Rejection

Claims 1-3, 5-56 were rejected under 35 U.S.C. §112, first paragraph, for lack of possession of the claimed invention. The rejection is respectfully traversed.

5                   Claim 1 was rejected for reciting "a component recognizing CD40". Claim 1 has been amended to recite the component recognizing CD40 is comprised of a bispecific antibody that recognizes CD40 and a fiber-knob protein of an adenovirus. Applicants submit that one of ordinary skill in the art would readily 10 recognize and use antibodies that bind specifically to CD40 and fiber-knob protein of an adenovirus. In view of the disclosed and recited binding specificities that have set forth the distinguishing characteristics of the claimed antibodies, Applicants submit that adequate written description commensurate to the scope of the claim 15 has been provided.

Claim 2 was rejected for reciting a fragment of antibody. The Examiner argued that it is unpredictable without undue experimentation to determine which fragment of certain antibody would function properly. Claim 2 has been incorporated into claim 1 20 which recites antigen-binding fragments of the claimed antibodies. Applicants submit that one of ordinary skill in the art would readily

recognize and use antigen-binding fragments such as Fab or sFv (single-chain antigen-binding protein) that can be made by methods generally known in the art (instant specification, page 29, lines 5-16). Hence, no undue experimentation is required to make and use 5 antigen-binding fragments of the claimed antibodies.

Claim 2 was also rejected for reciting fiber-knob protein of an adenovirus. The Examiner argued that there are many types of adenoviruses that have their own fiber-knob proteins which can induce many antibodies, and undue experimentation is required to 10 practice the present invention. Applicants respectfully disagree. Applicants submit that the present invention only requires an antibody that binds to the fiber-knob protein of an adenovirus regardless of the type or kind of adenovirus and fiber-knob protein, and one of ordinary skill in the art would readily recognize and use 15 such antibody according to the present invention. In view of the disclosed and recited binding specificities that have set forth the distinguishing characteristics of the claimed antibodies, Applicants submit that adequate written description commensurate to the scope of the claim has been provided.

20 Claim 31 was rejected for reciting "modification". Claim 31 has been amended to recite a genetically modified adenovirus

having a fiber protein comprising CD40 ligand. Two different strategies of such modifications were disclosed in Example 7. Firstly, a fiber chimera comprising a CD40L globular domain and a bacteriophage fibritin which replaces the natural fiber shaft was 5 disclosed. In the second strategy, only the fiber knob was replaced with the globular domain of CD40L. In view of the present disclosure and the known structure of adenoviral fiber protein readily available to one of ordinary skill in the art, Applicants submit that one of ordinary skill in the art would readily make and use the modified 10 adenovirus of the present invention. Furthermore, Applicants submit that the specification has provided adequate written description commensurate to the scope of the claims for the modified adenovirus.

15 Claims 1-56 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

The claims have been amended to recite a gene delivery system for CD40<sup>+</sup> immune cells or methods of manipulating CD40<sup>+</sup> 20 immune cells. Applicants submit that the specification has provided sufficient enablement for targeting to CD40<sup>+</sup> immune cells.

The Examiner argued that the specification fails to disclose a two-antibody modified or two-protein modified adenovirus system. Applicants respectfully disagree. Claim 1 is drawn to a gene delivery system comprising an adenovirus and a 5 bispecific antibody comprising a CD40-specific antibody and a fiber-knob protein-specific antibody. The specification had disclosed and provided sufficient enablement for the making and using of such targeting bispecific antibody comprising an anti-fiber-knob antibody and an anti-human CD40 antibody (Example 1) or anti-murine CD40 10 antibody (Example 3).

Claim 31 is drawn to a genetically modified adenovirus having a fiber protein comprising CD40 ligand. In one embodiment, the fiber shaft of the fiber protein is further replaced by bacteriophage T4 fibritin protein. Example 7 of the instant 15 specification teaches the making of these modified adenovirus. Firstly, a fiber chimera comprising a CD40L globular domain and a bacteriophage fibritin which replaces the natural fiber shaft was disclosed. Alternatively, only the fiber knob was replaced with the globular domain of CD40L (Example 7). Accordingly, Applicants 20 submit that the present specification has provided sufficient

enablement for the genetically modified CD40-targeted adenovirus as claimed herein.

The Examiner further rejected the claims for reading on *in vivo* and gene therapy methods. Applicants respectfully disagree.

5 The present invention discloses enhanced gene transfer to CD40<sup>+</sup> cells by retargeting the adenovirus to CD40. CD40-targeted virus demonstrated both dramatic and quantitative improvements in gene transfer compared to untargeted virus (Examples 1, 3-4). The claimed gene delivery systems also induce maturation of CD40<sup>+</sup> cells 10 as manifested by phenotypic and functional criteria (Examples 1, 3).

The present invention also teaches that dendritic cells genetically modified by the claimed targeted adenovirus can efficiently initiate antigen specific immunity towards tumor antigen (Example 3). It was also demonstrated that targeting of the 15 adenoviral vector to CD40 imparts an advantage in a vaccination context over untargeted adenoviral vectors. Such vaccinations retain their potency despite pre-immunization of animals with adenovirus infected dendritic cells (Example 3). Hence, Applicants submit that the present specification has provided sufficient enablement 20 commensurate in scope with the methods claimed. Accordingly,

Applicants respectfully submit that the rejection of claims 1-56 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 4 was rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 4 has been amended to identify the antibodies by their ATCC accession numbers as suggested by the Examiner. Accordingly, Applicants respectfully submit that the rejection of claim 4 under 35 U.S.C. §112, second paragraph, be withdrawn.

10                 Claims 2-4 were rejected under 35 U.S.C. §112, second paragraph, for reciting "a fragment thereof". Claim 2 has been canceled and is incorporated into claim 1 which does not recite the rejected phrase. Accordingly, Applicants respectfully submit that the rejection of claims 2-4 under 35 U.S.C. §112, second paragraph, be  
15 withdrawn.

Claims 11, 14, 17, 21, 40, 43, 53 and 54 were rejected under 35 U.S.C. §112, second paragraph, for reciting "such treatment". The claims have been amended to delete the phrase. Accordingly, Applicants respectfully submit that the rejection of  
20 claims 11, 14, 17, 21, 40, 43, 53 and 54 under 35 U.S.C. §112, second paragraph be withdrawn

Claims 11-30 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The rejection is respectfully traversed.

Claims 11 and 14 have been amended to recite a method of administering the gene delivery system of the present invention to CD40<sup>+</sup> cells, wherein said gene delivery system mediates gene transduction and causes maturation of said CD40<sup>+</sup> immune cells. Claims 17 and 21 have been amended to recite a method of administering the gene delivery system of the present invention to an individual, wherein said gene delivery system increases vaccination efficacy of CD40<sup>+</sup> dendritic cells in said individual. Applicants submit that the claims are complete and include active positive steps. Accordingly, Applicants respectfully submit that the rejection of claims 11-30 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claims 32 and 46 were rejected under 35 U.S.C. §112, second paragraph, for reciting "the fiber". Claims 32 and 46 have been amended to delete the phrase. Accordingly, Applicants respectfully submit that the rejection of claims 32 and 46 under 35 U.S.C. §112, second paragraph, be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claims 1, 5-7, 9-11, 13, 14, 16-18, 20-22, 24-31, 34-37, 40 and 42 were rejected under 35 U.S.C. §103(a) as being unpatentable over **Mendoza** et al. in view of **Christ** et al. The 5 rejection is respectfully traversed.

**Mendoza** et al. disclosed a plasmid vector encoding CD40 ligand could enhance immune responses to a transgene protein encoded by a co-injected plasmid DNA. **Christ** et al. taught gene therapy with adenovirus vectors. The Examiner argued that using 10 CD40 ligand to transduce dendritic cells for enhancing immune responses of genetic vaccination is known in the art as taught by **Mendoza** et al. Applicants respectfully disagree. **Mendoza** did not teach or suggest transduction of dendritic cells, nor did **Mendoza** et al. teach or suggest effects on CD40<sup>+</sup> or dendritic cells as shown in the 15 present invention.

Claim 1 is drawn to a gene delivery system comprising an adenovirus and a bispecific antibody conjugate which recognizes the viral fiber-knob protein and CD40 antigen. Neither **Mendoza** nor **Christ** teaches or suggests a gene delivery system for targeting 20 adenovirus to cell surface CD40 by the use of a bispecific antibody conjugate as claimed in the present invention. Hence, the combined

teaching of these two references does not provide a person having ordinary skill in this art with the motivation to produce Applicants' claimed gene delivery system with the expectation of successfully using such composition. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

The present invention is further drawn to methods of using the claimed gene delivery systems to genetically manipulate CD40<sup>+</sup> cells and to enhance dendritic cell-based vaccination. Neither 10 **Mendoze** nor **Christ** teaches or suggests methods of genetically manipulating CD40<sup>+</sup> cells or enhancing dendritic cell-based vaccination using CD40-targeted adenoviral vectors as claimed herein. **Mendoze** only taught plasmid DNA, and neither **Mendoze** nor **Christ** teaches or suggests teaching on plasmid DNA is applicable 15 to adenoviral vectors. One of ordinary skill in the art would not translate teaching on plasmid DNA to adenoviral vectors absent some suggestion or additional teaching.

In view of the above remarks, the combined teaching of **Mendoza** and **Christ** does not provide a person having ordinary skill in this art with the requisite expectation of successfully

use. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully submit that the rejection of claims 1, 5-7, 9-11, 13, 14, 16-18, 20-22, 24-31, 34-37, 40 and 42 5 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed June 20, 2001. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

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Respectfully submitted,

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**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**IN THE CLAIMS:**

Claims 2, 18, 22, 32 have been canceled.

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Claim 1 has been amended as follows:

1. (amended) A gene delivery system for ~~the genetic manipulation of~~ CD40<sup>+</sup> immune system cells, comprising:

(a) an adenovirus; and

10 (b) a component recognizing CD40 antigen comprising a first antibody, or antigen-binding fragment thereof, that binds to a fiber-knob protein of said adenovirus, wherein said first antibody or antigen-binding fragment thereof is attached to a second antibody, or antigen-binding fragment thereof, that binds to CD40 antigen.

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Claim 3 has been amended as follows:

3. (amended) The gene delivery system of claim 1 2, wherein said first antibody and second antibody are genetically fused together.

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Claim 4 has been amended as follows:

4. (amended) The gene delivery system of claim 1, wherein said antibody directed against CD40 antigen is secreted from hybridoma selected from the group consisting of G28.5 (ATCC #9110-5 HB) and FGK45.

Claim 5 has been amended as follows:

5. (amended) The gene delivery system of claim 1, wherein said gene delivery system mediates an effect genetic manipulation is selected from the group consisting of transduction of said CD40<sup>+</sup> immune cells, immunomodulation of said CD40<sup>+</sup> immune cells, and maturation of said CD40<sup>+</sup> immune cells.

Claim 9 has been amended as follows:

15 9. (amended) The gene delivery system of claim 1, wherein said CD40<sup>+</sup> immune system cells are selected from the group consisting of dendritic cells and B cells.

Claim 11 has been amended as follows:

20 11. (amended) A method for genetically manipulating CD40<sup>+</sup> immune system cells in an individual in need of such treatment comprising the step of:

administering the gene delivery system of claim 1 to said individual, wherein said gene delivery system mediates gene transduction and causes maturation of said immune cells.

5           Claim 14 has been amended as follows:

14. (amended) A method for genetically manipulating CD40<sup>+</sup> immune system cells in an individual in need of such treatment, comprising the step of:

10           administering the gene delivery system of claim 6 to said individual, wherein said gene delivery system mediates gene transduction and causes maturation of said immune cells.

Claim 17 has been amended as follows:

17. (amended) A method for enhancing dendritic cell-based vaccination immunotherapy in an individual in need of such treatment, comprising the step of:

15           administering the gene delivery system of claim 1 to said individual, wherein said gene delivery system increases vaccination efficacy of CD40<sup>+</sup> dendritic cells in said individual.

Claim 21 has been amended as follows:

21. (amended) A method for enhancing dendritic cell-based vaccination immunotherapy in an individual in need of such treatment, comprising the step of:

5 administering the gene delivery system of claim 6 to said individual, wherein said gene delivery system increases vaccination efficacy of CD40<sup>+</sup> dendritic cells in said individual.

Claim 31 has been amended as follows:

10 31. (amended) A recombinant adenoviral vector, comprising:

a genetically modified adenovirus having a fiber protein comprising CD40 ligand, wherein said CD40 ligand the modification targets said vector to CD40.

15 Claim 33 has been amended as follows:

33. (amended) The recombinant adenoviral vector of claim 31-32, wherein the fiber shaft of said fiber protein is replaced by bacteriophage T4 fibritin protein said first protein moiety is bacteriophage fibritin molecule, and wherein said second protein moiety is CD40 ligand

Claim 34 has been amended as follows:

34. (amended) A gene delivery system for CD40<sup>+</sup> ~~the genetic manipulation of immune system~~ cells, comprising:

5 the recombinant adenoviral vector of claim 31.

Claim 35 has been amended as follows:

35. (amended) The gene delivery system of claim 34, wherein said gene delivery system mediates an effect ~~genetic manipulation~~ is selected from the group consisting of transduction of said CD40<sup>+</sup> immune cells, immunomodulation of said CD40<sup>+</sup> immune cells, and maturation of said CD40<sup>+</sup> immune cells.

Claim 36 has been amended as follows:

15 36. (amended) The gene delivery system of claim 34, wherein said CD40<sup>+</sup> ~~immune system~~ cells are selected from the group consisting of dendritic cells and B cells.

Claim 40 has been amended as follows:

20 40. (amended) A method for enhancing dendritic cell-based vaccination immunotherapy in an individual in need of such treatment, comprising the step of:

administering the gene delivery system of claim 34 to said individual, wherein said gene delivery system increases vaccination efficacy of CD40<sup>+</sup> dendritic cells in said individual.

5           Claim 43 has been amended as follows:

43. (amended) A method for enhancing dendritic cell-based vaccination immunotherapy in an individual in need of such treatment, comprising the step of:

10           administering the gene delivery system of claim 38 to said individual, wherein said gene delivery system increases vaccination efficacy of CD40<sup>+</sup> dendritic cells in said individual.

Claim 46 has been amended as follows:

15           46. (amended) The recombinant adenoviral vector of claim 31, wherein said CD40 ligand comprises the ~~fiber knob domain of the adenovirus is replaced with~~ globular domain of CD40 ligand.

Claim 47 has been amended as follows:

20           47. (amended) A gene delivery system for CD40<sup>+</sup> ~~the genetic manipulation of immune system~~ cells, comprising:  
                  the recombinant adenoviral vector of claim 46

Claim 48 has been amended as follows:

48. (amended) The gene delivery system of claim 47, wherein said gene delivery system mediates an effect genetic manipulation is selected from the group consisting of transduction of said CD40<sup>+</sup> immune cells, immunomodulation of said CD40<sup>+</sup> immune cells, and maturation of said CD40<sup>+</sup> immune cells.

Claim 49 has been amended as follows:

10 49. (amended) The gene delivery system of claim 47, wherein said CD40<sup>+</sup> immune-system cells are selected from the group consisting of dendritic cells and B cells.

Claim 53 has been amended as follows:

15 53. (amended) A method for enhancing dendritic cell-based vaccination immunotherapy in an individual in need of such treatment, comprising the step:

20 administering the gene delivery system of claim 47 to said individual, wherein said gene delivery system increases vaccination efficacy of CD40<sup>+</sup> dendritic cells in said individual.

Claim 55 has been amended as follows:

55. (amended) A method for enhancing dendritic cell-based vaccination immunotherapy in an individual in need of such treatment, comprising the step:

5            administering the gene delivery system of claim 51 to said individual, wherein said gene delivery system increases vaccination efficacy of CD40<sup>+</sup> dendritic cells in said individual.